1,196,229

PATENT SPECIFICATION

NO DRAWINGS

1,196,229

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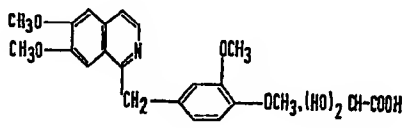
COMPLETE SPECIFICATION

Improvements in or relating to a New Glyoxylic Acid Salt, process for its preparation and Therapeutical Composition containing same

We, LABORATOIRES HOUDE, a French Body Corporate, residing at 15, rue Olivier Métra, 75 PARIS, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a new salt of glyoxylic acid and papaverine which possesses very interesting therapeutical properties as a spasmolytic, vaso-dilator and oxygen-saver at the level of the cells, that make it particularly useful for the treatment of arterial and venous circulatory disorders and in all cases where the oxydo-reduction metabolic processes within tissues are perturbed.

The new salt according to the invention, papaverine glyoxylate, has structural formula:



It has a molecular weight of 431.4 ($C_{22}H_{21}NO_8$). It is very readily soluble in water (which is a most advantageous property, especially with respect to papaverine hydrochloride which is poorly water-soluble), soluble in chloroform, very poorly soluble in ethanol and insoluble in ether. The pH of its 10% aqueous solution is 5.3.

Addition of ammonia to the aqueous solution causes precipitation of papaverine base. Papaverine glyoxylate dissolves in ethanol in the hot, however, papaverine base crystallizes on cooling. The aqueous solution exhibits the reactions characteristic of glyoxylic acid.

The invention relates also to a process for the preparation of papaverine glyoxylate comprising reacting together equimolar amounts of glyoxylic acid (advantageously monohydrated) and of papaverine. The reaction is carried out in the presence of an organic diluent inert toward the reagents and the reaction product, for example a ketone such as acetone or another non polar solvent.

The reaction is carried out, normally, at room temperature. After dissolution of the papaverine in the reaction medium, this is concentrated and the resulting papaverine glyoxylate is crystallized.

The following non limiting example illustrates the process according to the invention.

EXAMPLE

To a suspension of papaverine base (6.78 g, 0.02 mole) in acetone (70 ml) is added rapidly a solution of glyoxylic acid monohydrate (1.84 g, 0.02 mole) in acetone (20 ml). The mixture is stirred and the papaverine dissolves completely. Water (1 ml) is then added. The reaction mixture is concentration under reduced pressure, at low temperature, to a volume of about 25 ml; it is then cooled and crystallization is promoted by scratching and the reaction mixture is left overnight in the refrigerator. The reaction mixture is then suction filtered, washed repeatedly with a few ml (total of 12 ml) of ice-cold acetone and is dried in air to constant weight. This gives 6.65 g (yield 77.5%) by papaverine glyoxylate as a light sensitive white micro-crystalline powder. Melting point: 130°C with decomposition.

A few results of toxicological and pharmacological tests carried out with papaverine glyoxylate are given below for illustrative purposes.

I — *Acute toxicity*
LD_{50} in mice: i.v. 60 mg/kg
i.p. 200 mg/kg
per os 450 mg/kg

The LD_{50} of papaverine hydrochloride is 125 mg/kg by the intra-peritoneal route. Thus, papaverine glyoxylate is less toxic than the hydrochloride (200 mg of glyoxylate correspond to 175 mg of hydrochloride).

II — *Spasmolytic effects* (isolated ileum of guinea-pig)

1) Inhibition of barium chloride induced contractions by equimolecular concentrations of papaverine hydrochloride and glyoxylate:

Concentrations (as papaverine hydrochloride)	Inhibition %	
	papaverine hydrochloride	papaverine glyoxylate
5×10^{-6}	16	25
»	25	—
8×10^{-6}	20	34
»	42	60
»	40	55
9×10^{-6}	58	58
»	65	85
»	—	76
10^{-5}	68	72
»	75	86
»	62	—
2×10^{-5}	90	95
»	91	90

It is apparent from this table that the musculotropic spasmolytic activity of papaverine glyoxylate is at least equal to that of the hydrochloride; it appears even to be superior at low concentrations (8×10^{-6} to 10^{-5}).

2) Inhibition of histamine induced contractions:

2) Inhibition of histamine induced contractions:

Concentrations (as hydrochloride)	Inhibition %	
	papaverine hydrochloride	papaverine glyoxylate
0.8×10^{-6}	24	27
»	46	46
»	—	26
4.3×10^{-6}	60	92
»	70	92
»	43	70
»	63	89
»	75	95
»	90	95
»	85	90
»	67	76
Average	69.1	87.5

The spasmolytic activity of papaverine glyoxylate with respect to histamine is slightly superior to that of the hydrochloride at the concentration of 0.8×10^{-6} and markedly superior at 4.3×10^{-6} concentration.

3) Inhibition of acetylcholine induced contractions:

3) Inhibition of acetylcholine induced contractions:

Concentrations (as hydrochloride)	Inhibition %	
	papaverine hydrochloride	papaverine glyoxylate
0.8×10^{-6}	22	57
»	22	57
1.7×10^{-6}	41	76
4.3×10^{-6}	62	96
»	80	92
»	74	95
»	74	97
»	77	97

It is apparent from the above that the neurotropic spasmolytic activity of papaverine glyoxylate is very markedly superior to that of papaverine hydrochloride, while glyoxylic acid or its alkali metal salts have *per se* no spasmolytic action.

III — *Effects on cardia contractile strength in rabbits:*

A transcient decrease of contractile strength, followed by moderate inotropic action, is found on intravenous injection of 2 or 5 mg/kg of papaverine hydrochloride. After injection of equimolar dosages of papaverine glyoxylate, the decrease of contractile strength is much less substantial and is followed by a higher increase than after injection of the hydrochloride.

IV — *Protective effects against anoxia:*

The mean survival times of mice placed by lots of 10 in an exsiccator under vacuum are measured.

The percent increase of survival time is determined after intraperitoneal administration of equimolecular dosages of the compounds.

Papaverine glyoxylate was compared, in this test, with potassium glyoxylate and diisopropylamine glyoxylate.

The results are tabulated below.

	Survival time	Percent increase
Controls	119.3 sec.	
Potassium glyoxylate 50 mg/kg i.p.	128.2 sec.	7.5%
Papaverine glyoxylate 50 mg/kg i.p.	158.7 sec.	33%
Controls	137.7 sec.	
Diisopropylamine glyoxylate 50 mg/kg i.p.	79.5 sec.	42.3% decrease
Papaverine glyoxylate 50 mg/kg i.p.	151.4 sec.	+10%

The protective effects of papaverine glyoxylate against overall anoxia in mice are much more highly marked than those of potassium glyoxylate. In this test, diisopropylamine glyoxylate sensitizes mice to anoxia instead of protecting them.

The invention relates also to a therapeutical composition comprising, as active ingredient, papaverine glyoxylate and a pharmaceutically acceptable vehicle.

The composition according to the invention may be administered by the oral, parenteral or rectal route, the active ingredient being associated with the vehicles or excipients suitable for such routes of administration. In particular, it is formulated in the form of capsules, tablets, injectable solutions, suppositories, etc. Each unit dose contains advantageously 25 to 250 mg of active principle.

Non limiting examples of pharmaceutical forms of the composition are given below.

Capsules	
Papaverine glyoxylate	115 mg
Excipient: talc and magnesium stearate q.s. for a finished capsule	
Tablets	
Papaverine glyoxylate	150 mg
Excipient: lactose, talc and magnesium stearate q.s. for 1 tablet finished at about	0.25 g
Injectable solution	
Papaverine glyoxylate	50 mg
Sodium chloride	11 mg
Water for injectable preparations: q.s. for a 2 ml ampoule, sterilized by tyndallization.	
Suppositories	
Papaverine glyoxylate	180 mg
Semi-synthetic glycerides: q.s. for a 2 g suppository	

The composition according to the invention is useful for the treatment of cardiovascular diseases such as angina pectoris, arteriopathic conditions and venous insufficiencies of the lower limbs, and cerebral arteriosclerosis, of spasmodic conditions of the digestive tract such as gastritis, colitis, and hepatic colic, in urology for the treatment of nephrocolic, and vesical spasms, in gynoecology for the treatment of postpartum uterine colic, and of dysmenorrhea.

The usual dosage regimen is 50 mg to 1 g of active ingredient per 24 hours.

WHAT WE CLAIM IS:—

1. Papaverine glyoxylate.

2. A process for the preparation of papaverine glyoxylate comprising reacting together equimolar amounts of glyoxylic acid and of papaverine in the presence of an inert organic diluent and isolating the resulting papaverine glyoxylate.

3. A process as claimed in claim 2, wherein the organic diluent is a ketone.

4. A process as claimed in claim 3, wherein the ketone is acetone.

5. A process as claimed in any one of claims 2—4, wherein the papaverine glyoxylate is isolated by concentrating the reaction medium and crystallizing the salt on cooling.

6. A threapeutical composition containing, as active ingredient, papaverine glyoxylate and a pharmaceutically acceptable vehicle.

7. A therapeutical composition as claimed in claim 6, in unit dosage form.

8. A therapeutical composition as claimed in claim 7, wherein each unit dose contains 25—250 mg of active ingredient.

9. A therapeutical composition as claimed in claim 7 or 8, in the form of capsules or tablets.

10. A threapeutical composition as claimed in claim or 8, in the form of injectable solution.

11. A therapeutical composition as claimed in claim 7 or 8, in the form of suppositories.

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